PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 7/42, 7/44, 31/59
A61K 31/70, 31/715

A1

(11) International Publication Number: WO 91/19479

(43) International Publication Date: 26 December 1991 (26.12.91)

(21) International Application Number: PCT/US91/04436

(22) International Filing Date: 21 June 1991 (21.06.91)

(30) Priority data:

541,812	21 June 1990 (21.06.90)	US
541,813	21 June 1990 (21.06.90)	US
593,934	4 October 1990 (04.10.90)	US

(71) Applicant: TRUSTEES OF BOSTON UNIVERSITY [US/US]; 881 Commonwealth Avenue, Boston, MA 02115 (US).

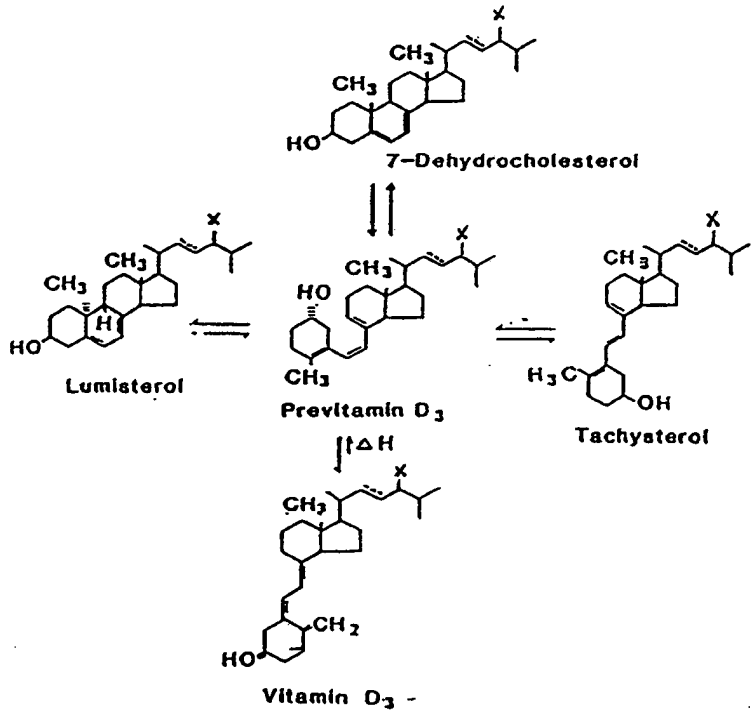
(72) Inventors: HOLICK, Michael, F. ; 31 Bishop Lane, Sudbury, MA 01776 (US). LU, Zhiren ; 871 Harrison Avenue, Boston, MA 02118 (US). TIAN, Xia, Quan ; 519 Park Drive, Apartment 7A, Boston, MA 02215 (US).

(74) Agents: GOLDSTEIN, Jorge, A. et al.; Sterne, Kessler, Goldstein & Fox, 1225 Connecticut Avenue, N.W., Suite 300, Washington, DC 20036 (US).

(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: COMPOSITIONS COMPRISING VITAMIN D PRECURSORS, ANALOGS THEREOF AND THEIR USE



(57) Abstract

Methods for providing active-type vitamin D compounds to an individual are disclosed. The individuals are exposed to sunlight to produce vitamin D and analogs or derivatives thereof via the skin. Pharmaceutical compositions comprising lumisterol and/or tachysterol and analogs or derivatives thereof are also disclosed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland			SN	Senegal
CI	Côte d'Ivoire	KR	Republic of Korea	SU	Soviet Union
CM	Cameroon	LI	Liechtenstein	TD	Chad
CS	Czechoslovakia	LK	Sri Lanka	TG	Togo
DE	Germany	LU	Luxembourg	US	United States of America
DK	Denmark	MC	Monaco		

TITLE OF THE INVENTION

COMPOSITIONS COMPRISING VITAMIN D PRECURSORS, ANALOGS THEREOF AND THEIR USE

Field of the Invention

The invention is in the field of cosmetics and medicinal chemistry. In particular, the present invention relates to topical compositions which provide vitamin D, derivatives and analogs thereof throughout the year. In another aspect, the present invention relates to a method of producing previtamin D, derivatives and analogs thereof. The topical compositions of the invention allow a user in the high northern and southern latitudes to produce previtamin D, derivatives and analogs thereof in and on their skin even when exposed to low energy sunlight in the winter as well as in the morning and evening throughout the year. The method employs tachysterol and lumisterol, derivatives and analogs thereof which photoisomerize to previtamin D, derivatives and analogs therof, respectively, when exposed to low levels of ultraviolet radiation.

Background of the Invention

Vitamin D_3 is a derivative of provitamin D_3 (7-dehydrocholesterol), the immediate biological precursor of cholesterol. With adequate exposure to sunlight, dietary supplements are not normally required. Holick et al. in Braunwald et al., Harrison's Principles of Internal Medicine, 11th ed. McGraw-Hill (1987), pp. 1857-69. However, not all

individuals are exposed to the adequate levels of sunlight, especially in the winter.

When skin is exposed to sunlight or artificial sources of ultraviolet (UV) radiation, the UV radiation penetrates the epidermis and causes a variety of biochemical reactions. Included in these reactions are the transformation of provitamin D_3 to vitamin D_3. The electromagnetic energy having wavelengths between 290 and 315 nm is absorbed by provitamin D_3 resulting in its fragmentation to previtamin D_3. Although previtamin D_3 is biologically inert, it is thermally labile and spontaneously undergoes a temperature-dependent rearrangement to form the thermally stable vitamin D_3. After biosynthesis, vitamin D_3 is translocated from the epidermis into the circulation via a vitamin-D binding protein. Holick et al., Science 211:590-593 (1981); Holick et al. in Braunwald et al., Harrison's Principles of Internal Medicine, 11th ed., McGraw-Hill (1987), pp. 1857-69.

Factors that are frequently considered as affecting the cutaneous synthesis of vitamin D_3 include age, altitude, geographical location, time of day and area of exposure to sunlight. Common to most of these factors is the availability of the requisite amount of ultraviolet radiation with energies between 290 and 315 nm which is necessary to convert provitamin D_3 to vitamin D_3. MacLaughlin et al., Science 216:1001-1003 (1982).

The availability of vitamin D precursor in the skin and its photo-induced transformation to previtamin D_3 and then to vitamin D_3 is an efficient

physiological source of and mechanism for the replenishment of vitamin D_3. However, during the winter in northern latitudes, sunlight does not contain enough high energy ultraviolet radiation to convert provitamin D_3 (7-dehydrocholesterol) in human skin to previtamin D_3 (Webb, Kline and Holick, J. Clin. Endocrinol Met. 67:373-378 (1988)). As a result, individuals in these latitudes cannot make vitamin D_3 in their skin, even when they are exposed to sunlight. The lack of adequate exposure to ultraviolet radiation gives rise to the possibility of serious vitamin D deficiency, a breakdown in blood calcium regulation with concomitant hypocalcemia and bone calcium wasting.

The availability of the vitamin D precursor in the skin and its photo-induced transformation to previtamin D_3, and then to vitamin D_3, is an efficient physiological source of, and mechanism for the replenishment of vitamin D_3. Previously, it was thought that the only method of producing previtamin D_3 was to transform provitamin D_3. This transformation requires sunlight or artificial UV light in the region of 290-315 nm. Therefore, in areas where the available light energy is below this range (wavelengths greater than 316 nm), the transformation does not occur to any significant extent. Kobayashi et al., J. Nutr. Sci. Vitaminol. 19:123 (1973).

It has been disclosed (Holick, M., Transactions of the Association of American Physicians, 42:54-63 (1979); Molecular Endocrinology; MacIntyre and Szelke, eds.; Elsevier/North Holland Biomedical Press (1979), pp.301-308) that the topical application of

hydroxylated metabolites of provitamin D compounds to the skin combined with U.V. phototherapy is a method for the sustained administration of vitamin D metabolites to patients who suffer vitamin D metabolic disorders. When the hydroxylated provitamins are applied and irradiated with ultraviolet radiation, they convert to hydroxylated previtamins which then thermally isomerize to the hydroxylated vitamin D. This work is also disclosed in Holick et al., New England Journal of Medicine 301:349-354 (1980) and U.S. Patent No. 4,310,511 (Jan. 12, 1982).

1,25-Dihydroxyvitamin D3 and its analogs have been shown to be powerful antiproliferative agents which are effective for the treatment of the hyperproliferative disorder psoriasis (DeLuca, H. Fed. Proc. Am. Soc. Biol. 2:224-236 (1988); Holick in DeGroot et al., Endocrinology 2:902-926, Grune and Stratton, N.Y., N.Y., (1988); Morimoto et al., Br. J. Dermatol. 115:421-429 (1986); Holick, Arch. Dermatol. 125:1692-1697 (1989)).

Hungarian Patent No. 102,939 discloses cosmetic creams containing provitamin D (such as ergosterol) which, when irradiated with ultraviolet rays, are transformed into vitamin D.

MacLaughlin et al., Science 216:1001-1003 (1982), disclose the synthesis of previtamin D_3 from provitamin D_3 in human skin and in an organic solvent after exposure to narrow-band radiation or simulated solar radiation. When human skin or an organic solvent containing provitamin D_3 were exposed to 295 nm radiation, up to 65% of the provitamin D_3 was converted to previtamin D_3. The authors further disclose that

the optimum wavelength for the production of previtamin D_3 is between 295 nm and 300 nm.

Dauben et al., J. Am. Chem. Soc. 104:5780-5781 (1982); J. Am. Chem. Soc. 104:355-356 (1982), disclose the effect of wavelength on the photochemistry of provitamin D_3 and the effect of wavelength on the production of previtamin D_3. The authors found that when provitamin D_3 is exposed to light in the range of 254 nm, it is converted to a variety of photoproducts, the major portion being about 75% tachysterol. This mixture was then exposed to either 300 nm of light, broad-band 350 nm light or 355 nm light to give a build up of previtamin D_3. Dauben et al. conclude that if provitamin D_3 is first irradiated at 0°C with 254 nm light to give a quasi photostationary state of provitamin D_3, previtamin D_3, tachysterol and lumisterol, and the mixture is thereafter irradiated (0°C) with 350 nm light, a maximum of 83% previtamin D_3 is produced.

Malatesta et al., J. Amer. Chem. Soc. 103:6781-6783 (1981), disclose the effects of different UV wavelengths on the relative quantities of photoproducts produced from provitamin D_3.

Holick et al. disclose that the photochemical conversion of previtamin D_3 to lumisterol and tachysterol is the major factor that prevents vitamin D_3 intoxication after a single prolonged exposure to the sun. Holick et al., Science 211:590-592 (1981). The corollary to this finding is that lumisterol and tachysterol are two biologically inert products thought to be sloughed off the skin during the natural turnover of the epidermal cells.

Provitamin D_2 (ergosterol) is the precursor of vitamin D_2. Vitamin D_2 is one of the major forms of vitamin D that is used to fortify foods such as milk and multivitamins.

SUMMARY OF THE INVENTION

The present invention is related to the discovery that topical formulations comprising lumisterol and tachysterol, analogs and derivatives thereof are effective means of providing previtamin D, derivatives and analogs thereof to individuals. The present invention utilizes the low energy UV photoconversion of lumisterol and tachysterol, analogs or derivatives thereof, to previtamin D, analogs or derivatives thereof, respectfully, as a method of producing vitamin D, analogs or derivatives thereof in the skin. It is this novel finding that solves the problem of producing vitamin D compounds via the skin in areas of low energy sunlight.

In particular, the invention is directed to lumisterol and tachysterol, derivatives and analogs thereof which are convertible to vitamin D analogs in the presence of low energy UV light. The invention is also directed to pharmaceutical compositions containing an effective amount of lumisterol and/or tachysterol, derivatives or analogs thereof, and a pharmaceutically effective carrier.

The invention is also directed to a method for providing vitamin D, analogs or derivatives thereof, to an individual by administering to the individual a pharmaceutical composition of the invention.

The invention is also directed to a method of treating hyperproliferative disorders of the skin including psoriasis, healing wounds and inhibiting scar formation with the pharmaceutical compositions of the invention.

The invention is also directed to the treatment of ulcers such as diabetic ulcers of the feet, decubitus ulcers (bed sores), genito-urinary ulcers, and ulcerative keratitis with the pharmaceutical compositions of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the photochemical conversion of provitamin D to vitamin D and the concomitant production of lumisterol and tachysterol. When the bond between C-22 and C-23 is a single covalent bond and X is hydrogen, the compounds belong to the D_3 family, e.g. vitamin D_3. Where the bond between C-22 and C-23 is a double covalent bond and X is methyl, the compounds belong to the D_2 family, e.g. vitamin D_2.

Figure 2 depicts an HPLC trace of a control solution of provitamin D_3 (A) and a solution of provitamin D_3 exposed to sunlight on a day during the winter (B).

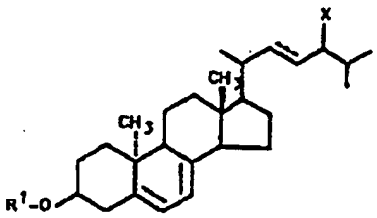
Figure 3 depicts an HPLC trace of a control solution of tachysterol (A) and a solution of tachysterol exposed to sunlight on a day during the winter (B).

Figure 4 depicts an HPLC trace of a control solution of lumisterol (A) and a solution of

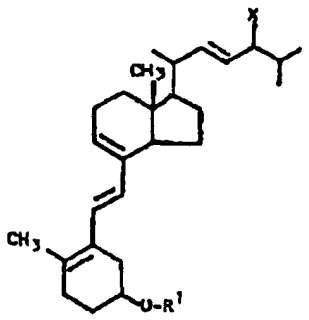
lumisterol exposed to sunlight on a day during the winter (B).

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The active compounds utilized in the present invention are tachysterol, lumisterol and derivatives thereof, either alone or in combination. The tachysterol and lumisterol derivatives have the following Formulae (I) and (II), respectively:



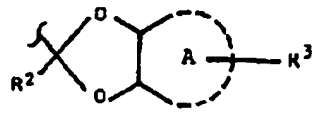
(I)



(II)

wherein the bond between C-22 and C-23 is a single or double bond;
X is hydrogen, methyl or ethyl; and

R^1 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue, or R^1 is an orthoester glycoside moiety of the Formula (III):



(III)

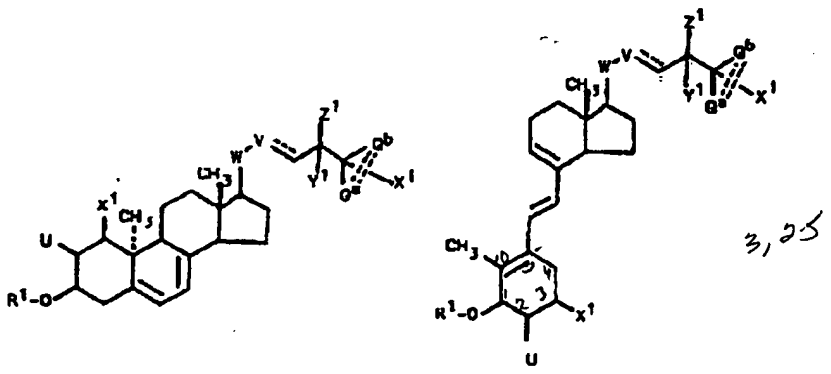
where A represents a glucofuranosyl or a glucopyranosyl ring;

R^2 is hydrogen, lower (C_1-C_4) alkyl, C_7-C_{10} aralkyl, or C_6-C_{10} aryl; and

R_3 is hydrogen or a straight or branch chain glycosidic residue containing 1-20 glycosidic units per residue.

These compounds are photoisomers of previtamin D, the precursor of biologically active vitamin D. Tachysterol and lumisterol may be prepared by photoisomerization and isolation as disclosed by Holick et al., Biochem. 18:1003-1008 (1979). Analogous methods for making the corresponding glycosidic and orthoester glycoside derivatives are taught, for example, by Holick et al., U.S. Patent Nos. 4,410,515 and 4,521,410, the disclosures of which are fully incorporated by reference herein.

The tachysterol and lumisterol analogs of the present invention have the following Formulae (IV) and (V), respectively:



(IV) (V)

wherein the bond between carbons C-22 and C-23 is single or double bond;

Y^1 is hydrogen, F, CH_3, CH_2CH_3 or X^1;

U is hydrogen, -OH or -O-(C_2-C_4 alkyl)-OH;

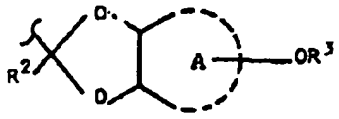
Z^1 is F, H or X^1;

Q^a is CF_3 or CH_2X^1;

Q^b is CF_3 or CH_3;

wherein X^1 is selected from the group consisting of hydrogen, -OH and OR^1;

wherein R^1 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue, or R^1 is an orthoester glycoside moiety of the Formula (III):



(III)

wherein A represents a glucofuranosyl or glucopyranosyl ring;

R^2 is hydrogen, lower C_1-C_4 alkyl or aryl, with the proviso that aryl is phenyl or phenyl substituted by chloro, fluoro, bromo, iodo, lower C_1-C_4 alkyl, C_1-C_4 alkoxy; or naphthyl; and

R^3 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue;

W is CH-CH_3 or O;

V is CH_2 or O;

with the proviso that both W and V are not both O; and

"===" is either a single bond between Q^a and Q^b or a hydrogen atom on Q^a and Q^b.

These compounds are photoisomers of previtamin D analogs, the precursor of biologically active vitamin D analogs.

Examples of particular vitamin D analogs are taught, for example, by Holick et al., U.S. Patent No. 4,310,511 (Jan. 12, 1982); Partridge et al., U.S. Patent No. 4,634,692 (1987); Yamada, JP Publication No. J5 5111-460; DeLuca et al., U.S. Patent No. 4,719,205 (1988); Holick et al., U.S. Patent No. 4,410,515 (1983); Holick et al., U.S. Patent No. 4,521,410 (1985); Holick et al., U.S. Patent No. 4,230,701; and Shiina et al., Arch. Biochem. Biophys. 220:90 (1983), the disclosures of which are fully incorporated by reference herein. Methods for making the corresponding glycosidic and orthoester glycoside vitamin D analogs are taught, for example, by Holick et al., U.S. Patent Nos. 4,410,515 and 4,521,410, the disclosures of which are fully incorporated by reference herein.

The tachysterol and lumisterol analogs may be prepared by photoisomerization of the requisite provitamin D analog according to the method disclosed by Holick et al., Biochem. 18:1003-1008 (1979).

By administering an effective amount of tachysterol, lumisterol and analogs or derivatives thereof in topical compositions according to this invention, it is possible for the first time to provide a method which allows individuals living in

regions of low energy sunlight to produce vitamin D compounds via their skin, thus preventing harmful vitamin D_3 depletion. The compositions of the present invention may be used, therefore, in methods of treating or preventing osteomalacia due to vitamin D deficiency, and calcium disorders resulting from a lack of vitamin D (a lack of vitamin D leads to deficient intestinal absorption of calcium which results in hypocalcemia), glucocorticoid-induced decrease in calcium absorption, osteoporosis, senile decrease in calcium absorption, hypoparathyroidism, milk fever disease, turkey weak leg disease, etc.

The present invention also provides for a method of healing wounds and inhibiting scar formation and treating hyperproliferative disorders of the skin including psoriasis by administering an effective amount of a tachysterol or luminsterol analog of the invention. Wounds to the external epithelium include cuts, punctures and lacerations, including corneal lacerations. The invention also provides for the treatment of ulcers such as diabetic ulcers of the feet, decubitus ulcers (bed sores), genito-urinary ulcers, and ulcerative keratitis by administering an effective amount of a tachysterol or luminsterol analog of the invention. Ulcerative keratitis is caused, for example, by extended wear of contact lenses.

Genito-urinary ulcers treatable with the tachysterol and lumisterol analogs of the invention include those caused by, for example, herpes simplex virus as well as other viral, fungal and bacterial infections. See Harrison's Principles of Internal

Medicine, E. Braunwald et al. (eds.); McGraw-Hill Book Co., New York, N.Y., 1987, pp. 514-516.

Examples of tachysterol and lumisterol analogs include 1-hydroxytachysterol$_2$, 1-hydroxytachysterol$_3$, 1-hydroxylumisterol$_2$, 1-hydroxylumisterol$_3$, 1,24-dihydroxytachysterol$_2$, 1,24-dihydroxytachysterol$_3$, 1,24-dihydroxylumisterol$_2$, 1,24-dihydroxylumisterol$_3$, 1,25-dihydroxytachysterol$_2$, 1,25-dihydroxytachysterol$_3$, 1,25-dihydroxylumisterol$_2$, 1,25-dihydroxylumisterol$_3$, 24,25-dihydroxytachysterol$_2$, 24,25-dihydroxytachysterol$_3$, 24,25-dihydroxylumisterol$_2$, 24,25-dihydroxylumisterol$_3$, 25,26-dihydroxytachysterol$_2$, 25,26-dihydroxytachysterol$_3$, 25,26-dihydroxylumisterol$_2$, 25,26-dihydroxylumisterol$_3$, 1,24,25-trihydroxytachysterol$_2$, 1,24,25-trihydroxytachysterol$_3$, 1,24,25-trihydroxylumisterol$_2$, 1,24,25-trihydroxylumisterol$_3$, 2-ß-(3-hydroxypropoxy)-1 alpha,25-dihydroxytachysterol$_2$, 2-ß-(3-hydroxypropoxy)-1 alpha,25-dihydroxytachysterol$_3$, 2-ß-(3-hydroxypropoxy)-1 alpha,25-dihydroxylumisterol$_2$, 2-ß-(3-hydroxypropoxy)-1 alpha,25-dihydroxylumisterol$_3$, as well as the side chain fluoro derivatives of 1,25-dihydroxytachysterol$_2$, 1,25-dihydroxytachysterol$_3$, 1,25-dihydroxylumisterol$_2$, 1,25-dihydroxylumisterol$_3$, 1-hydroxytachysterol$_2$, 1-hydroxytachysterol$_3$, 1-hydroxylumisterol$_2$, and 1-hydroxylumisterol$_3$. Also included are the 20- and 22-oxa tachysterol and lumisterol derivatives including 20-oxa-1α(OH)tachysterol$_2$, 20-oxa-1α(OH)tachysterol$_3$, 20-oxa-1α(OH)lumisterol$_2$, 20-oxa-1α(OH)lumisterol$_3$, 20-oxa-1α,25(OH)$_2$tachysterol$_2$, 20-oxa-1α,25(OH)$_2$tachysterol$_3$, 20-oxa-1α,25(OH)$_2$lumisterol$_2$, 20-oxa-1α,25(OH)$_2$-

lumisterol$_3$, 22-oxa-1α(OH)tachysterol$_2$, 22-oxa-1α(OH)tachysterol$_3$, 22-oxa-1α(OH)lumisterol$_2$, 22-oxa-1α(OH)lumisterol$_3$, 22-oxa-1α,25(OH)$_2$tachysterol$_2$, 22-oxa-1α,25(OH)$_2$tachysterol$_3$, 22-oxa-1α,25(OH)$_2$lumisterol$_2$ and 22-oxa-1α,25(OH)$_2$lumisterol$_3$. Also included within the scope of the present invention are 25,26 cyclopropyl compounds including 1,24-dihydroxy-25,26-dehydrotachysterol$_3$, 1,24-dihydroxy-25,26-dehydrotachysterol$_2$, 1,24-dihydroxy-25,26-dehydrolumisterol$_3$, and 1,24-dihydroxy-25,26-dehydrolumisterol$_2$.

Foremost among the individuals which may be treated with the compositions of the invention are humans, although the invention is not intended to be so limited. Any animal which may benefit from treatment with the compositions of the invention are within the spirit and scope of the present invention.

By using tachysterol and lumisterol analogs in topical compositions according to this invention, it is possible for the first time to provide a method which allows individuals living in regions of low sunlight to produce vitamin D analogs via their skin. The compositions of the present invention may be used, therefore, in methods of treating decubitus and diabetic foot ulcers; ulcerative keratitis; treating psoriasis; wound healing; inhibiting scar formation; treating or preventing osteodystrophy due to an acquired or inherited disorder in vitamin D metabolism; glucocorticoid-induced decrease in calcium absorption; osteoporosis; senile decrease in calcium absorption; hypoparathyroidism; milk fever disease; and turkey weak leg disease.

The compounds of the present invention can be administered in any appropriate pharmacological carrier for topical or intravenous administration. The dosage administered will be dependent on the age, health and weight of the recipient, and the nature of the effect desired.

The topical compositions of the invention may be applied so that at least 0.1 microgram, preferably at least about 10 micrograms to about 100 mg of the vitamin D precursor/gm carrier is administered to the skin. A preferred range is between about 1 microgram to about 1 milligram of tachysterol, lumisterol or analog or derivative thereof/gm carrier.

The compositions of the invention formulated for intravenous administration may comprise at least about 0.1 microgram, preferably at least about 1.0 microgram to about 100 mg of the vitamin D precursor or analog precursor per ml of physiologically acceptable solution. A most preferred range is about 1.0 micrograms to about 100 micrograms of tachysterol, lumisterol or analog or derivative thereof per ml of solution.

The compounds can be employed in a pharmacologically inert topical carrier such as one comprising a gel, an ointment or a cream, including such carriers as water, glycerol, alcohol, propylene glycol, fatty alcohols, triglycerides, fatty acid esters or mineral oils. Other possible carriers are liquid petrolatum, isopropylpalmitate, polyethylene glycol ethanol 95%, polyoxyethylene monolaurate 5% in water, sodium lauryl sulfate 5% in water, and the like. Minerals such as

anti-oxidants, humectants, viscosity stabilizers and the like may be added, if necessary.

Alternatively, the compounds may be employed as part of a sun screen lotion which selectively screens the harmful high energy UV radiation (below 315 nm) but which allows medium and low energy UV radiation (above 315 nm) to pass which is of sufficient energy to photoisomerize lumisterol, tachysterol and the analogs or derivatives thereof to previtamin D or the analogs or derivatives thereof. Alternatively, the compounds of the invention may be added to broad range sun screens that absorb radiation with energies of up to 360 nm. Such sun screen lotions may comprise any of those well known to those of ordinary skill in the art, for example, ethyl p-aminobenzoate (benzocaine), p-aminobenzoic acid (PABA), octyl methoxycinnamate (PARASOL^R MCX), butyl methoxydibenzoylmethane (PARASOL^R 1789), phenyl salicylate (salcol), 2-ethoxyethyl p-methoxycinnamate, glyceryl p-aminobenzoate, 2,4-dibenzoyl resorcinol, octyl dimethyl PABA, oxybenzone, benzophenones, methyl anthranilate, cinoxate, amyldimethyl PABA, homomenthyl salicylate, digalloyl trioleate, ethyl-p-glycosylimido benzoate, and red veterinary petrolatum. For other examples, see Algra et al., Int. J. Derm. 17:628-634 (1978), Sayre, R.M. et al., Photochem.Photobiol. 29:559-566 (1979).

Preparations for parenteral administration include sterile or aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers

include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers, such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present, such as, for example, antimicrobials, anti-oxidants, chelating agents, inert gases and the like. See, generally, Remington's Pharmaceutical Science, 16th Ed., Mack Eds., 1980.

The compositions comprising tachysterol and/or lumisterol and analogs or derivatives thereof which are formulated for parenteral administration may be utilized to provide an individual with these vitamin D analog precursors so as to allow the production of vitamin D analogs or derivatives in the skin in the presence of medium and low energy UV radiation.

The invention further relates to solutions comprising the tachysterol and lumisterol, analogs and derivatives thereof which may be exposed to UV radiation to allow the preparation of a solution comprising an active vitamin D compound as desired just before administration to the individual. This method avoids the decomposition of vitamin D and analogs thereof which occurs in solution. Solutions which may comprise compounds of the invention may include the above-listed parenteral solutions. Of course, the solutions comprising the lumisterol and tachysterol analogs must be stored in an opaque

container to avoid premature conversion of tachysterol and lumisterol analogs to the corresponding vitamin D analog.

Having now generally described this invention, the same will be understood by reference to an example which is provided herein for purposes of illustration only and is not intending to be limited unless otherwise specified.

Example 1

Crystalline provitamin D_3 was dissolved in methanol at a concentration of 10 micrograms/ml. Ten ml of this solution was placed in quartz test tubes. One test tube containing provitamin D_3 in methanol was exposed to direct sunlight in Boston during November, 1989 between 9 AM and 10 AM (Fig. 2B) while a similar sample remained in the dark over the same period of time (Fig. 2A). At the end of the exposure, a small aliquot was taken from each test tube and chromatographed on a high performance liquid chromatograph according to MacLaughlin et al., Science 216:1001-1003 (1982). Similar studies were conducted with lumisterol (Fig. 4) and tachysterol (Fig. 3) that were prepared as previously described (Holick et al., Biochem. 18:1003-1008 (1979). The analysis of all the chromatograms in Figs. 2-4 revealed that when tachysterol and lumisterol were exposed to sunlight in November between 9 and 10 AM, they underwent photoisomerization to previtamin D_3 (Figs. 3B, 4B). In contrast, provitamin D_3 exposed to the same direct sunlight did not convert to previtamin D_3 (Fig. 2B). All samples that were kept in the dark for the same

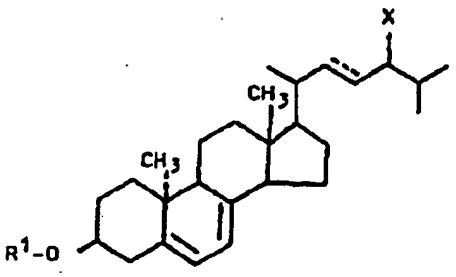
time did not convert to previtamin D_3 (Figs. 2A, 3A, 4A).

It is expected that the tachysterol and lumisterol analogs of the present invention, upon irradiation with the same low intensity and energy UV light, will give the corresponding analogs.

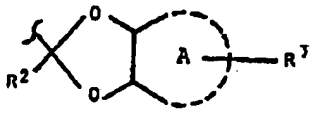
Having now generally described this invention, it will be apparent to one of ordinary skill in the art that the same can be carried out in a variety of embodiments and variations which are equivalent without affecting the spirit or scope of the invention or any embodiments thereof.

WHAT IS CLAIMED IS:

1. A composition comprising a pharmaceutically acceptable carrier and a compound of the formula



wherein the bond between C-22 and C-23 is a single or double bond;
X is hydrogen, methyl or ethyl; and
R^1 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue, or R^1 is an orthoester glycoside moiety of the formula:



where A represents a glucofuranosyl or a glucopyranosyl ring;

R^2 is hydrogen, lower (C_1-C_4) alkyl, C_7-C_{10} aralkyl, or C_6-C_{10} aryl; and

R_3 is hydrogen or a straight or branch chain glycosidic residue containing 1-20 glycosidic units per residue;

wherein said compound is presentin an amount effective to provide vitamin D_3 when said composition is administered to an individual.

2. The composition of claim 1, wherein said compound is lumisterol$_3$.

3. The composition of claim 1, wherein said carrier is effective for topical administration.

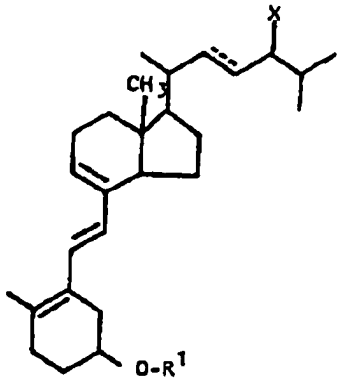
4. The composition of claim 3, further comprising one or more sun screen agents.

5. The composition of claim 1, wherein said carrier is effective for parenteral administration.

6. The composition of claim 1, wherein said compound is present in an amount of 0.00001 to 10% by weight.

7. The composition of claim 1, wherein said compound is present in an amount of 0.0001 to 0.01% by weight.

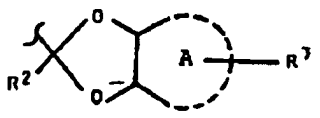
8. A composition a pharmaceutically acceptable carrier and a compound having the formula:



wherein the bond between C-22 and C-23 is a single or double bond;

X is hydrogen, methyl or ethyl; and

R^1 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue, or R^1 is an orthoester glycoside moiety of the formula:



where A represents a glucofuranosyl or a glucopyranosyl ring;

R^2 is hydrogen, lower (C_1-C_4) alkyl, C_7-C_{10} aralkyl, or C_6-C_{10} aryl; and

R_3 is hydrogen or a straight or branch chain glycosidic residue containing 1-20 glycosidic units per residue;

wherein said compound is present in an amount effective to provide vitamin D_3 when said composition is administered to an individual.

9. The composition of claim 8, wherein said compound is tachysterol$_3$.

10. The composition of claim 8, wherein said carrier is effective for topical administration.

11. The composition of claim 10, further comprising one or more sun screen agents.

12. The composition of claim 8, wherein said carrier is effective for parenteral administration.

13. The composition of claim 8, wherein said compound is present in an amount of 0.00001 to 10% by weight.

14. The composition of claim 8, wherein said compound is present in an amount of 0.0001 to 0.01% by weight.

15. A composition comprising lumisterol and tachysterol and a pharmaceutically acceptable carrier wherein said lumisterol and tachysterol are present in an amount effective to provide vitamin D_3 when said composition is administered to an individual.

16. The composition of claim 15, wherein said carrier is effective for topical administration.

17. The composition of claim 15, wherein said carrier is effective for parenteral administration.

18. The composition of claim 15, wherein said lumisterol and tachysterol are individually present in an amount of from 0.00001 to 10% by weight.

19. The composition of claim 15, wherein said lumisterol and tachysterol are individually present in an amount of from 0.001 to 0.01% by weight.

20. A method for providing vitamin D_3 to an individual which comprises administering to said individual the pharmaceutical composition of any one of claims 1, 8 and 15 and exposing said individual to UV radiation.

21. The method of claim 20, wherein said composition is administered by topical means.

22. The method of claim 21, wherein said composition further comprises one or more sun screen agents.

23. The method of claim 20, wherein said composition is administered by intravenous means.

24. The method of claim 20, wherein said UV radiation is provided by sunlight of insufficient intensity and wavelength to effect the conversion of provitamin D to vitamin D.

25. The method of claim 24, wherein said UV radiation has a wavelength above 315 nm.

26. A method for treating or preventing osteomalacia due to vitamin D deficiency or a calcium disorder resulting from a lack of vitamin D, glucocorticoid-induced decrease in calcium absorption, osteoporosis, senile decrease in calcium absorption, hypoparathyroidism, milk fever disease, or turkey weak leg disease in an individual which comprises administering to said individual the pharmaceutical composition of any one of claims 1, 8 and 15 and exposing said individual to low energy UV radiation.

27. The method of claim 26, wherein said composition is administered by topical means.

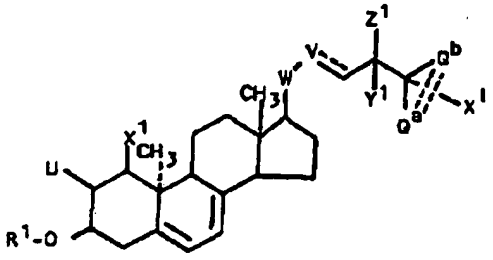
28. The method of claim 27, wherein said composition further comprises one or more sun screen agents.

29. The method of claim 26, wherein said composition is administered by intravenous means.

30. The method of claim 26, wherein said UV radiation is provided by sunlight of insufficient intensity and wave-length to effect the conversion of provitamin D to vitamin D.

31. The method of claim 30, wherein said UV radiation has a wavelength above 315 nm.

32. A composition comprising a pharmaceutically acceptable carrier and a compound of the formula



wherein the bond between carbons C-22 and C-23 is single or double bond;

Y^1 is hydrogen, F, CH_3, CH_2CH_3 or X^1;

U is hydrogen, -OH or -O-(C_2-C_4 alkyl)-OH;

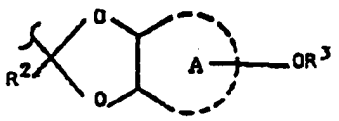
Z^1 is F, H or X^1;

Q^a is CF_3 or CH_2X^1;

Q^b is CF_3 or CH_3;

wherein X^1 is selected from the group consisting of hydrogen, -OH and OR^1;

wherein R^1 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue, or R^1 is an orthoester glycoside moiety of the formula:



wherein A represents a glucofuranosyl or glucopyranosyl ring;

R^2 is hydrogen, lower alkyl, or aryl, with the proviso that aryl is phenyl or phenyl substituted by chloro, fluoro, bromo, iodo, lower C_1-C_4 alkyl, C_1-C_4 alkoxy; or naphthyl; and

R^3 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue;

W is $CH\text{-}CH_3$ or O;

V is CH_2 or O;

with the proviso that both W and V are not both O; and

"═══" is either a single bond between Q^a and Q^b or a hydrogen atom on Q^a and Q^b;

wherein said compound is present in an amount effective to provide a vitamin D analog when said composition is administered to an individual.

33. The composition of claim 32, wherein said compound is 1alpha,25-dihydroxylumisterol$_3$, 1alpha,25-dihydroxylumisterol$_2$, 1alpha-hydroxylumisterol$_3$, 1alpha-hydroxylumisterol$_2$, 24,25-dihydroxylumisterol$_3$,

24,25-dihydroxylumisterol$_2$, 1,24-dihydroxylumisterol$_3$, 1,24-dihydroxylumisterol$_2$, and 1,24-dihydroxy-25,26-dehydrolumisterol$_3$.

34. The composition of claim 34, wherein said carrier is effective for topical administration.

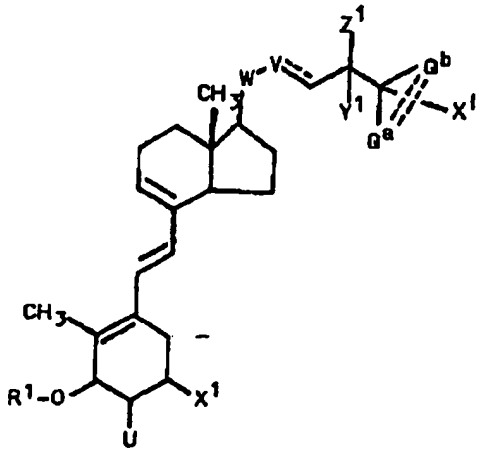
35. The composition of claim 32, further comprising one or more sun screen agents.

36. The composition of claim 32, wherein said carrier is effective for parenteral administration.

37. The composition of claim 32, wherein said compound is present in an amount of 0.00001 to 10% by weight.

38. The composition of claim 32, wherein said compound is present in an amount of 0.0001 to 0.01% by weight.

39. A composition comprising a pharmaceutically acceptable carrier and a compound having the formula:



wherein the bond between carbons C-22 and C-23 is single or double bond;

Y^1 is hydrogen, F, CH_3, CH_2CH_3 or X^1;

U is hydrogen, -OH or -O-(C_2-C_4 alkyl)-OH;

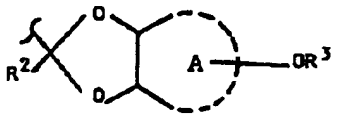
Z^1 is F, H or X^1;

Q^a is CF_3 or CH_2X^1;

Q^b is CF_3 or CH_3;

wherein X^1 is selected from the group consisting of hydrogen, -OH and OR^1;

wherein R^1 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue, or R^1 is an orthoester glycoside moiety of the Formula (III):



wherein A represents a glucofuranosyl or glucopyranosyl ring;

R^2 is hydrogen, lower alkyl, aralkyl, or aryl, with the proviso that aryl is phenyl or phenyl substituted by chloro, fluoro, bromo, iodo, lower C_1-C_4 alkyl, C_1-C_4 alkoxy; or naphthyl; and

R^3 is hydrogen or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue;

W is CH-CH_3 or O;

V is CH_2 or O;

with the proviso that both W and V are not both O; and

"----" is either a single bond between Q^a and Q^b or a hydrogen atom on Q^a and Q^b;

wherein said compound is present in an amount effective to provide a vitamin D analog when said composition is administered to an individual.

40. The composition of claim 39, wherein said compound is 1alpha,25-dihydroxytachysterol$_3$, 1alpha,25-dihydroxytachysterol$_2$, 1alpha-hydroxytachysterol$_3$, 1alpha-hydroxytachysterol$_2$, 24,25-dihydroxytachysterol$_3$, 24,25-dihydroxytachysterol$_2$, 1,24-dihydroxytachysterol$_3$, 1,24-dihydroxytachysterol$_2$, and 1,24-dihydroxy-25,26-dehydrotachysterol$_3$.

41. The composition of claim 39, wherein said carrier is effective for topical administration.

42. The composition of claim 41, further comprising one or more sun screen agents.

43. The composition of claim 39, wherein said carrier is effective for parenteral administration.

44. The composition of claim 39, wherein said compound is present in an amount of 0.00001 to 10% by weight.

45. The composition of claim 39, wherein said compound is present in an amount of 0.0001 to 0.01% by weight.

46. A method for providing a vitamin D analog to an individual which comprises administering to said individual the composition of claim 32 or 39 and exposing said individual to UV radiation.

47. The method of claim 46, wherein said composition is administered by topical means.

48. The method of claim 47, wherein said composition further comprises one or more sun screen agents.

49. The method of claim 46, wherein said composition is administered by intravenous means.

50. The method of claim 46, wherein said UV radiation is provided by sunlight of insufficient intensity and wavelength to effect the conversion of the corresponding provitamin D analog to the vitamin D analog.

51. The method of claim 46, wherein said UV radiation has a wavelength above 315 nm.

52. A method for treating decubitus or diabetic foot ulcers; ulcerative keratitis; psoriasis; wounds; inhibiting scar formation; glucocorticoid-induced decrease in calcium absorption; osteoporosis; senile decrease in calcium absorption; hypoparathyroidism; milk fever disease; turkey weak leg disease or treating or preventing osteodystrophy due to an acquired or inherited defect in the metabolism of

vitamin D; which comprises administering to said individual the composition of claim 32 or 39 and exposing said individual to UV radiation.

53. The method of claim 52, wherein said composition is administered by topical means.

54. The method of claim 53, wherein said composition further comprises one or more sun screen agents.

55. The method of claim 52, wherein said composition is administered by intravenous means.

56. The method of claim 52, wherein said UV radiation is provided by sunlight of insufficient intensity and wave-length to effect the conversion of the corresponding provitamin D analog to the vitamin D analog.

57. The method of claim 56, wherein said UV radiation has a wavelength above 315 nm.

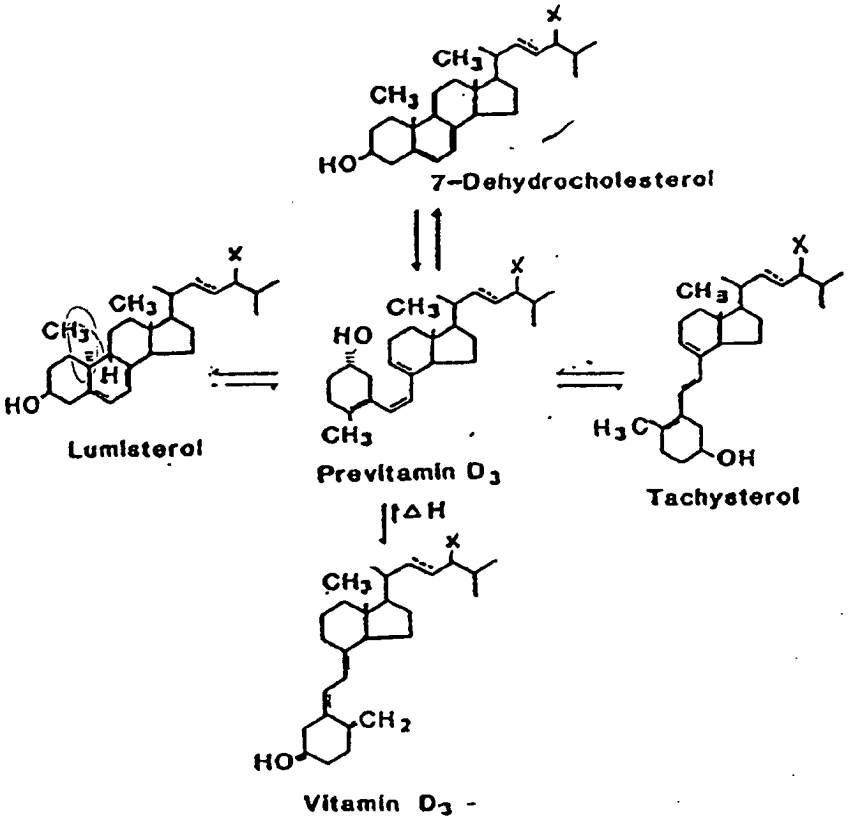
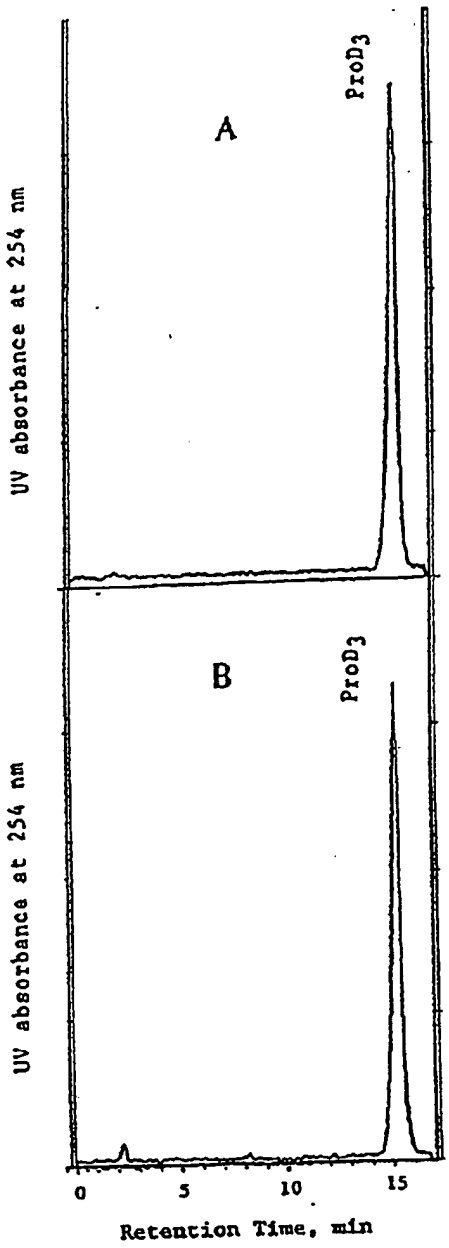
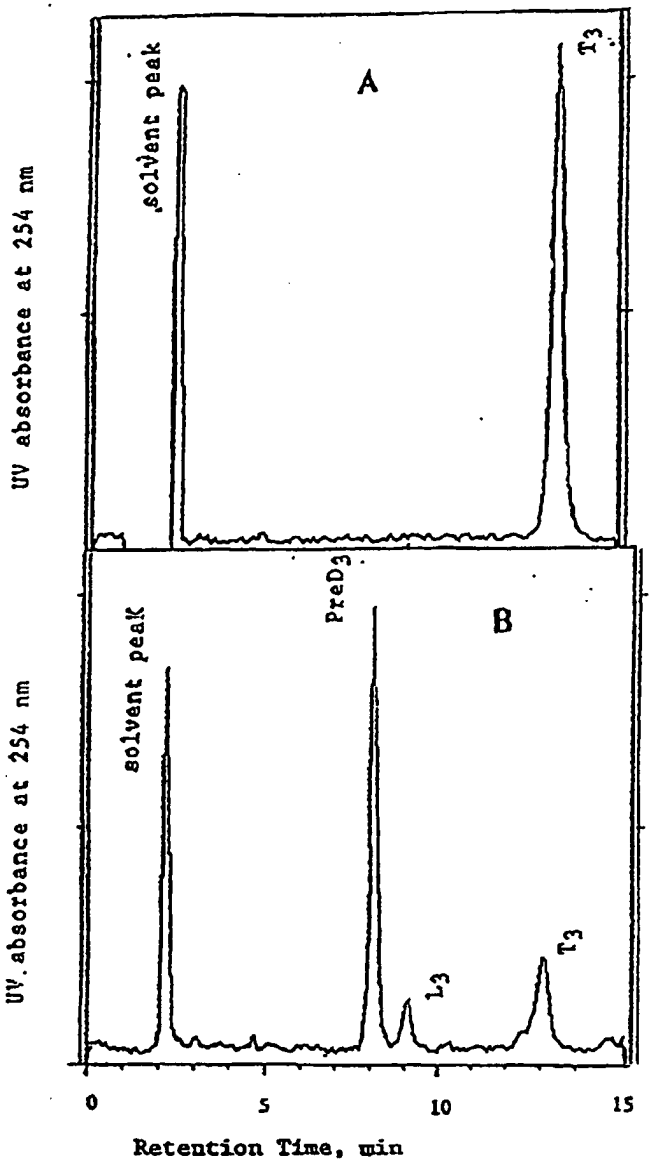

7-Dehydrocholesterol
Lumisterol
Previtamin D_3
Tachysterol
Vitamin D_3

FIGURE 1



Exposure of ProvitaminD_3(ProD_3) (10 µg/ml) to Sunlight on Nov.11, 1989 between 9:00-10:00 AM
A - Control, B - Exposed

FIGURE 2

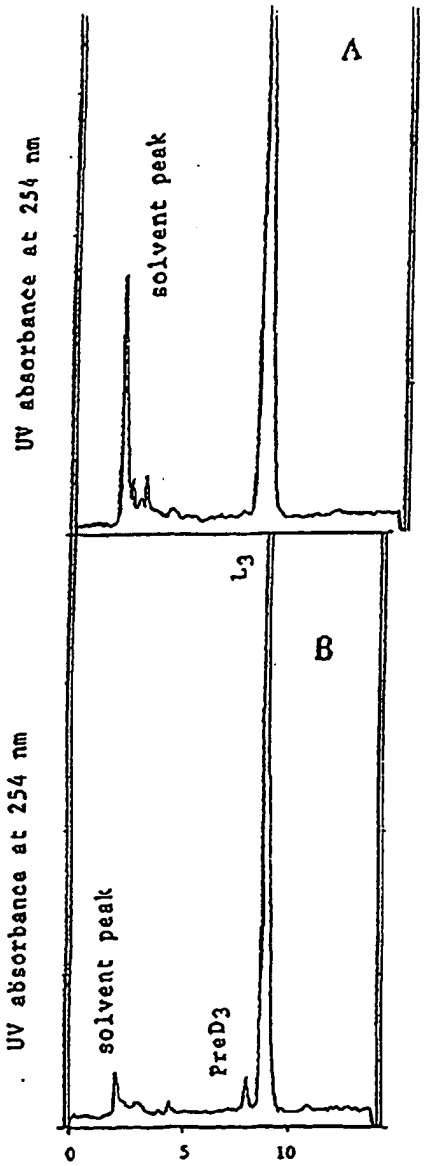


Exposure of Tachysterol$_3$(T_3)(10 µg/ml) to Sunlight on Nov.11,1989 between 9:00-10:00 AM

A - Control, B - Exposed

$PreD_3$ - Previtamin D_3; T_3- Tachysterol$_3$

FIGURE 3



Exposure of Lumisterol$_3$(L_3) (10 µg/ml) to Sunlight on Nov.11, 1989 between 9:00-10:00 AM
A - Control, B - Exposed

FIGURE 4

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/04436

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61K 7/42,44 31/59,70,715
US CL : 424/59,60 514,25,54,167,171

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	424/59,60 514/25,54,167,171

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

APS,CAS Online, Derwent:Compounds of the claims with terms such as SUNSCREEN, VITAMIN D, VITAMIN D DEFICIENCY, OSTEOMALACIA, OSTEOPOROSIS, CALCIUM, HYPOPARATHYROIDISM,WOUND, ULCER,DIABETES

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US, A, 3,702,810 (DE LUCA ET AL.) 14 NOVEMBER 1972 See column 1, lines 15-23.	8-14,39-45
A	US, A, 4,230,701 (HOLICK ET AL.) 28 OCTOBER 1980 See entire document.	1-57
Y	US, A, 4,310,511 (HOLICK) 12 JANUARY 1982 See column 10, lines 10-67.	1-7,20-38, 46-57
Y	US, A, 4,335,120 (HOLICK ET AL.) 15 JUNE 1982 See column 2, line 40-column 4, line 49; column 6, lines 33-56.	1-57

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28 OCTOBER 1991	07 NOV 1991
International Searching Authority	**Signature of Authorized Officer**
ISA/US	NGUYEN NGOC-HO INTERNATIONAL DIVISION KIMBERLY JORDAN

Form PCT/ISA/210 (second sheet) (Rev.11-87)